REMARKS/ARGUMENTS

Claims 27-31, 33, 34, 36-46, 48, 49, 51-55, 57, 58, 60-62, 64, 65, 75, 76, 78, 79, 81 and 82 remain in this application. Claims 28, 36, 53, 54, 55, 60, 61, and 62 have been amended.

The amendments are made responsive to the rejections under 35 U.S.C. 112 as set out in paragraph 5 on page 5 of the Office Action. Claim 28 has now been amended to recite two steps: (i) a step of administering intradermally to the patient the peptide represented by SEQ. ID. No. 1 and, optionally, one or more further specified peptides presenting T cell $CD4^+$ epitopes and (ii) detecting whether the administered peptide(s) cause(s) an observable delayed-type hypersensitivity response. Claim 28 as amended explicitly recites all the essential steps for carrying out an *in vivo* skin test type diagnostic method as described in the description from line 12 on page 8 to line 2 on page 9.

The dependency of claim 36 has been amended to render it more correctly dependent only on claim 27, which is directed to *in vitro* assays.

Since no separate rejection under 35 U.S. C. 112 has been raised against any of claims 29–31, 33, 34, 36-38, 41 and 43, it is believed that the amendment of claim 28 also suffices to remove rejection under 35 U.S. C. 112 against all these claims.

Claim 53 is intended to cover a variant version of the method according to claim 28 wherein the chosen peptide(s) are provided *in vivo* by provision of polynucleotides encoding the peptide(s). Responsive to the Examiner's comment particularly in relation to the term "expressing" in previous claim 53, that claim has now been amended to refer to a first step of "administering intradermally one or more polynucleotides which encode in human cells the peptide represented by SEQ. ID. NO:1 and, optionally, one or more further peptides selected from the group consisting of the peptides represented by SEQ. ID. Nos: 2 to 11." New claim 53 also recites a second detecting step as in new claim 28. Support for new claim 53 is to be found in the description starting at line 2 on page 8 to line 2 on page 9.

Claims 54, 55, 60 to 62 have been amended for consistency with new claim 53 by substitution of "expressing" by " which encodes". It is believed that these amendments render moot the rejection under 35 U.S.C. 112 against all of claims 54, 55, 57, 58, 60-62, 64 and 65.

Argument against rejection under 35 U.S.C. 102(e) based on Andersen et al.

The Andersen et al. US Patent cited by the Examiner is based on

International Application PCT/DK94/00273 (published as WO 95/01441 on 12th January 1995). It cannot rightly, however, be seen as disclosing the invention now claimed, or rendering it obvious, since it **does not direct the selection of the peptide ES1 (the N-terminal 15 amino acid fragment of the *M. tuberculosis* protein ESAT-6) for diagnostic use in humans.** This is the peptide represented by SEQ. ID. NO: 1 in the subject application and the essential peptide specified in claim 1.

Indeed, no prior art document before the Examiner points to use of that peptide for determining *M. tuberculosis* infection in humans. In contrast, it is noted once again that the subject application emphasizes at lines 24 to 25 on page 1 of the description that peptide ES1 alone was found to detect nearly 60% of TB patients tested. As previously emphasized in the Response to the Restriction Requirement, this is comparable with a conventional skin test without the problem of false negatives arising from previous BCG vaccination (see in the description line 1 on page 21 and lines 1 to 3 on page 22). Thus, while it may be considered preferable to combine peptide ES1 with further ESAT-6 epitope-containing fragments to provide a peptide panel enabling even higher percentage detection of TB patients, it is evident that peptide ES1 alone enables a clinically useful and indeed advantageous method for detecting *M. tuberculosis* infection in humans compared to conventional TB diagnosis.

The Andersen et al. US Patent teaches purification of ESAT-6 from a crude culture filtrate and includes reference to diagnostic use but includes no more than very general speculation about diagnostic use of ESAT-6 fragments. Disclosure of the amino acid sequence of ESAT-6 *per se* is not a disclosure of any particular fragment or fragments for any diagnostic use. Moreover, the only relevant example, Example 6 merely reports skin testing of purified whole ESAT-6 in guinea pigs. The specification provides no teaching whatsoever of assistance in selecting T cell epitope-containing peptides for diagnostic use in humans. It certainly does not direct selection of the N-terminal peptide ES1.

In this connection, the Examiner is asked to note again the disclosure of Elhay et al., Infect. Immun. (July 1998) 66 3454-3456 (first cited in the search report for the Paent International Application and discussed in the Response to the Restriction Requirement beginning at the bottom paragraph on page 6). That paper (copy appended for ease of reference) derives from the same research group as the

Andersen et al US Patent. It is emphasized again that D7 provides data showing that a peptide from the C-terminal region of ESAT-6, peptide p8, is effective in a skin test in detecting T cells in guinea pigs infected with *M. tuberculosis*. However, in the same studies peptide p1 (amino acid residues 1-20 of ESAT-6) gave no significant result. It is simply not possible to extrapolate from any prior art animal studies that any fragment from the N-terminus of ESAT-6 will be a useful diagnostic tool in humans. The Elhay et al. paper was published more than 3 years after WO 95/01441 and 2 years after Brandt et al. (also previously discussed in the Response to the Restriction Requirement) and yet merely gives indication that a good diagnostic reagent for a human skin test is a combination of whole ESAT-6 with another whole protein (see in D7 the paragraph beginning in column 1 on page 3455 and the sentence immediately preceding that paragraph). D7 thus fully supports that Andersen et al were not in possession of the invention now claimed at the 102 (e) date applicable to the Andersen et al US Patent or even far later. If anything, D7 and WO 95/01441 provide prior art teaching which points directly away from use of any N-terminal peptide of ESAT-6 in the context of TB diagnosis!

In view of the amendments and foregoing remarks it is believed that the application is now in condition for allowance and respectfully solicits a Notice of Allowance.

The Commissioner is hereby authorized to charge payment of any fees required associated with this communication or credit any overpayment to Deposit Account No. 50-0337. If an extension of time is required, please consider this a petition therefor and charge any additional fees which may be required to Deposit Account No. 50-0337. A duplicate copy of this page is enclosed.

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